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SHOULD VITAMIN D BE GIVEN ONLY TO INFANTS?

VITAMIN D has been so successful in preventing rickets during i fancy that there has been little emphasis on continuing its use aft the second year.

But now a careful histologic study has been made which reve a startlingly high incidence of rickets in children 2 to 14 years ol Follis, Jackson, Eliot, and Park* report that postmortem examin tion of 230 children of this age group showed the total prevalen of rickets to be 46.5%.

Rachitic changes were present as late as the fourteenth year, a the incidence was higher among children dying from acute disea than in those dying of chronic disease.

The authors conclude, "We doubt if slight degrees of ricket such as we found in many of our children, interfere with heal and development, but our studies as a whole afford reason to pr long administration of vitamin D to the age limit of our study, t fourteenth year, and especially indicate the necessity to suspect a to take the necessary measures to guard against rickets in si children."

*R. H. Follis, D. Jackson, M. M. Eliot, and E. A. Park: Prevalence of rickets in childr between two and fourteen years of age, Am. J. Dis. Child. 66:1-11, July 19

LUPUS ERYTHEMATOSUS DISSEMINATA

Case Report No. 32

Dr. Frederic Burke R. S.—43-9553

R. S., an eight year old colored girl was admitted to the Children's Hospital on December 9, 1943, with the chief complaint of hematuria. Three weeks prior to this admission, she had been discharged from Freedman's Hospital, Washington, D. C., where she had been a patient for one month. A summary of the findings of that institution follows:

Chief complaints:

1. Intermittent swelling and pain in joints for five months.
2. Intermittent low grade fever for five months.
3. Generalized chest and precordial pain for three weeks.
4. Axillary and inguinal adenopathy for three weeks.

The patient had been in good health until five months prior to admission when she developed insidious complaints of pain and swelling of her left arm and hand; later the other upper extremity became involved. Edema of the face and lower extremities were noted. The joint involvement, characterized by remissions and exacerbations, was accompanied by a low grade fever (up to 102°). Three weeks before, glandular enlargements were noted in the axillae and inguinal regions. She was referred for hospitalization by a private physician with the tentative diagnosis of Hodgkin's disease, glomerulonephritis or rheumatic fever.

At that time, she was a well developed, well nourished colored female in no apparent distress. The cheeks presented a reddened discoloration of "butterfly" configuration. Moderate non-tender discrete generalized lymphadenopathy, moderate injection of throat and tonsils, dental caries, diminished breath sounds in the left lung base, slightly enlarged heart and normal pulse and blood pressure were noted. The abdomen was full with shifting dullness and the liver edge was barely palpable. There was edema of the hands and feet and passive motion of her left elbow caused pain.

Laboratory Data

1. Urinalyses were negative.
2. Erythrocytes—3,860,000; Leucocytes numbered 14,000 with 87% polymorphonuclears.
3. Hinton and Eagle tests negative.
4. Sed. rate 5 m.m./hr.; NPN: 27.1 mgms.%.
5. Tuberculin test P.P.D. #2; positive.
6. Circulation time 9 seconds, venous pressure normal.

7. Blood cultures, agglutination tests, sickle cell smears, complement fixation tests, skin tests for Trichinosis and EKG were all negative.
8. X-ray of the chest was essentially negative.
9. Biopsy of lymph glands revealed only hyperplasia.
10. Biopsy of skeletal muscle revealed no evidence of pathology.
11. Heterophile antibody test (Paul-Bunnell) was positive in dilutions 1:448.

Treatment was symptomatic. The glands diminished somewhat in size and she was released as asymptomatic after four weeks. Diagnosis upon discharge was recorded as Infectious Mononucleosis on the basis of lymphadenopathy and positive heterophile antibody tests. Tuberculosis (probably inactive) on the basis of the skin test was a second impression.

Three weeks later she was admitted to the Children's Hospital complaining of gross blood in her urine. A week before she had developed a generalized red rash on the back of her hands and trunk and a day or so later became "swollen all over" and had two or three episodes of hemoptysis. The rash had disappeared just before admission. The significant findings at this time were; mild edema of the face, eyelids and extremities; palpable liver (two centimeters below the costal margin) and a distended abdomen with general dullness upon percussion especially in the flanks. Coarse rales in the left base with diminished breath sounds in this area were noted. The heart was greatly enlarged to percussion but there were no murmurs nor disturbances of rhythm. There was stiffening of the elbow joints upon extension of the arms. Healed scars were noted in the right axilla and above the pubis. Generalized moderate non-tender discrete lymphadenopathy was present.

An x-ray of the chest showed the heart to be greatly enlarged (possibly with pericardial effusion). In spite of a negative urinalysis upon admission, the initial impression was acute glomerulo-nephritis with cardiac involvement. This diagnosis seemed to be supported a few days later by the findings of albuminuria, hematuria and diminution of the heart size after six days bed rest. The P.P.D. gave a strongly positive result. Her temperature upon admission was 100.2° and remained low grade until the seventh day when it arose to 104.4° and for the following week was septic in character, rising every afternoon between 102.4° and 103.6°, usually returning to normal in the evening. Blood cultures taken during this time were negative. This same undulating type of fever was present throughout her entire hospital stay. Arterial and venous pressure readings repeatedly were normal. The heterophile antibody test (Paul-Bunnell) repeated at this hospital was weakly positive (1–56).

She was given symptomatic treatment including an empirical course of sulfadiazine after the first week for the septic type of fever. After a few days she began complaining bitterly of transient, migratory pains

about her ankles, hands and arms; this was exhibited mostly at night time and was intermittent throughout her course. Motion of the joints particularly was painful although redness and swelling were never observed. Aspirin and phenobarbital usually gave prompt relief from this pain temporarily.

An electrocardiagram, taken when the heart was dilated, showed evidence of an abnormal myocardium by a very low T 1 and T a and inverted T 3. This examination was repeated two weeks later and a normal record was noted. On four or five occasions an ill-defined reticular urticarial type of rash appeared over the extremities and the trunk lasting for a period of from a few hours to two days. Daily urinalyses showed massive amounts of albumen varying from twenty to three thousand mgms. per cent. Usually a few red blood cells, casts and white blood cells were reported. Numerous hemograms showed a mild anemia with white blood-counts ranging between 6,500 and 14,000 with a slight predominance of polymorphonuclear cells. Eosinophils appeared ranging between one and four per cent. Innoculation of a guinea pig with the patient's urine gave a negative result and agglutination tests for typhoid, paratyphoid, typhus and brucellosis were negative.

Repeated Kahn and Wassermann tests were positive although quantitatively their titres did not rise. Anti-luetic therapy was withheld until a month before death when she was given a course of bismuth injections. Teleoroentgenograms showed her heart to significantly enlarge and reduce in size on three different occasions without apparent cause. Sedimentation rates were moderately rapid, ranging between 27–34 m.m./hr. An attempt to precipitate a rash by exposure to ultra-violet light failed and she pursued a chronic course with exacerbations and remissions of edema, arthralgia and fever.

An abdominal paracentesis was performed on May 26, 1944, and 1200 cc of greenish transparent fluid removed. This fluid produced negative cultures. The following day the child developed a high fever, evidence of peritonitis and expired.

Necropsy Summary

Dr. Robert Sullivan: The body was that of a well developed and fairly well nourished colored female child of about seven years. There was moderate edema of the face and the axillary nodes were enlarged, discrete and firm. The abdomen was distended.

Areas of bronchopneumonia were scattered irregularly throughout both lungs. The visceral and parietal pericardium were lightly adherent over a small portion of the right ventricle. The heart was slightly enlarged. On the interior leaflet of the tricuspid valve there were two slightly elevated areas of pinhead size and also a grayish-yellow vegetation 2 millimeters in

diameter which was attached to the papillary muscle of this leaflet. When the aortic cusp of the mitral valve was reflected a number of grayish-yellow verrucae were noted. The appearance was similar to that described by Libman and Sacks as atypical verrucous endocarditis.

The peritoneal cavity contained about 400 cubic centimeters of cloudy yellow, foul smelling fluid from which Streptococcus hemolyticus was cultured. The peritoneal surfaces of all the viscera were covered by a yellow purulent exudate. The spleen was three times its normal weight; there was marked thickening of the capsule and the cut surface was bright red with marked increase in the fibrous tissue elements. The kidneys were both markedly enlarged. The capsules stripped with a slightly increased resistance leaving smooth gray surfaces with scattered irregular hemorrhagic appearing areas. The cut surfaces were pale with many hemorrhagic, beefy looking portions.

The microscopic and gross findings indicated a pericarditis, myocarditis and endocarditis of a low grade type. The peritonitis, which was of an acute type, presumably followed the abdominal paracentesis. There were perivascular round cell infiltrations about the vessels of both the liver and heart with an increase in fibrous tissue which may have been part of the same process. The marked changes noted in the spleen were believed to be due to a healed tuberculosis. The kidneys together with the heart and spleen seemed to have born the brunt of organic damage. The first named organs were the sites of a chronic and subacute diffuse glomerulonephritis. There was little, if any, evidence of the "wire loop" lesions in the glomeruli. Throughout practically all of the organs were found evidences of connective tissue degenerative changes which were believed to be compatible with the findings noted in disseminated lupus erythematosus.

The pathological diagnosis was as follows: Acute purulent peritonitis; chronic glomerulo-nephritis; early acute pericarditis; atypical verrucous endocarditis; bronchopneumonia; chronic spleenitis and perispleenitis; generalized lymphadenopathy; fatty infiltration of the liver.

Probable cause of death: Acute peritonitis and acute disseminated lupus erythematosus (11).

Discussion

Dr. Frederic G. Burke: Lupus erythematosus disseminata is a systemic disease of unknown etiology that is characterized by many and varied manifestations involving almost every tissue and organ in the body, particularly the heart, blood vessels, lymph nodes, blood, kidneys and serous surfaces in addition to the skin.

Since Kaposi's (2) original description of this disease in 1872 there have been 284 cases reported in the literature, only nine of which occurred in

patients under the age of ten years. All of these nine cases were white children. We believe this is the first reported case of lupus erythematosus disseminata in a colored child.

Klemperer, Pollack and Baehr (3) (1941) and Fox and Rosahn (4) (1943) have written excellent accounts of the pathologic changes found in this disease and Cluxton and Krause (1) (1943) have written a good review of its clinical aspects.

This case is illustrative of the bizarre variety of symptoms and signs that characterize the syndrome known as lupus erythematosus disseminata. The recent literature contains the bulk of the reported cases but little has been done to clarify its etiology or pathogenesis. Early writers on the subject believed the tubercle bacillus to be the cause, but the failure to demonstrate any evidence of tuberculosis in many instances makes this theory untenable. The association of tuberculosis, healed or active in many of the reported cases, however, is not to be dismissed as a chance association. The possibility of an "allergic" sensitizing influence of tuberculin among other foreign proteins remains. Fox (5) reported a case which presumably developed as the result of an injection of horse serum. O'Leary (6), Pels (7), Roxburgh (8) believe the disease results from sensitization by bacterial toxins, particularly streptococci and tubercle bacilli. This patient demonstrated a markedly positive reaction to the tuberculin skin test and at autopsy had presumptive evidence of healed tubercles in the spleen.

The rarity of this syndrome in the colored race (only five cases occuring in negros appear in the literature) has not been explained. This is especially noteworthy when the high incidence of tuberculosis in this race is considered. It is interesting to speculate that a measure of protection is given this group by the increased pigmentation of their skin to the sensitizing influence of actinic rays. An attempt to induce an exacerbation of the skin rash in this colored child, as suggested by Wilson (9), was a failure.

It is generally considered that a lowered white blood cell count is a characteristic feature of lupus erythematosus disseminata but leucocytosis is not an infrequent finding, especially in the presence of secondary infections. Leucopenia was absent in this case. Only one-third of the 65 cases observed at the Massachusetts General Hospital had leucopenia (Bauer) (10).

The appearance of falsely positive Wassermann and Kahn tests have been frequently noted in this disease. The lack of any clinical evidence of syphilis and the consistency of the quantitative titers attested to the falsity of this reaction in our patient. Of particular interest in this case was the remarkable recurrence of dilatation of the heart. Upon at least two occasions while under observation her heart enlarged well beyond

50% of the transverse diameter of the chest as revealed by serial x-rays, diminishing in size each time in about two to three weeks. The existence of transient myocardial damage during one of these episodes of dilatation was confirmed by electrocardiographic evidence. Cardiac decompensation was not complete, however, since the venous pressure remained within normal limits. Direct examination of the heart revealed extensive damage to the pericardium, myocardium, and endocardium. Small endocardial verrucae, such as were described by Libman and Sacks, were grossly visible and microscopic proliferation of connective tissue in the endocardium was present. Klemperer, Pollack and Baehr (3) in a detailed report of their study of twenty cases, found macroscopic evidence of endocardial vegetation in 40% and microscopic evidence of endocardial lesions in an additional 20%.

The significance of the positive Paul-Bunnell test for heterophile antibodies (1:448) during the first month of this patient's symptoms is not known, although it may represent, like the Wassermann and Kahn reports, a false reaction.

Treatment was symptomatic in the absence of any known effective therapy. The mortality rate of this disease is high. The average duration of life after the appearance of symptoms is 18 months, death not infrequently resulting from some complication. The patient reported expired 12 months after the onset and the cause of death was an intercurrent generalized peritonitis.

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(11) Dr. Paul Klemperer of Mt. Sinai Hospital, New York City, reviewed the microscopic sections of the kidney and did not believe they were particularly characteristic of lupus.

SPECIAL REPORT

IDIOPATHIC THROMBOCYTOPENIC PURPURA[1]

Dr. Eudell G. Paul

Definition

Idiopathic thrombocytopenic purpura or Werlhof's disease is a blood dyscrasia existing in either acute or chronic stages and characterized by reduced numbers of thrombocytes in the blood stream which lead to the formation of various subcutaneous and submucous hemorrhages. At the present time the etiology of this condition is unknown.

Incidence

This condition is essentially a disease of children for it is in this group that purpura hemorrhagica first manifests itself in most instances; but, as in other diseases, the age limit may well extend into adolescence and in a small percentage of cases into later years. Girls are said to be afflicted more frequently than boys. However, in a review of a series of 18 cases in 1944–45 at The Children's Hospital, Washington, D. C., it was found that 12 were boys and 6 were girls. Finn (1) found a similar ratio of 2:1 in favor of boys. A family history of easy bruising was present in 16 per cent of these 18 cases. The age limits in this series ranged from 14 days old to 14½ years. Seventeen of these patients were white children and one was a 6 year old colored boy.

Etiology

Much has been done to ascertain the causative agent or factors responsible for this condition. The answer appears to lie in the discovery of some thrombocytolytic substance or bone marrow depressant (whose action is specific upon the megakaryocytes). Troland and Lee (2) call attention to a substance they termed "thrombocytopen" which when injected into the blood stream of rabbits, produces a reduction in the number of thrombocytes. They obtained it by making extracts of spleens removed from patients with essential thrombocytopenic purpura. This substance is probably present in other reticulo-endothelial tissue, also. How it acts and what it is has not been determined. These writers mention that sometimes a drug like allylisopropylacetylcarbamide causes a reduction in platelets.

[1] This paper was submitted in competition for the Mead Johnson Prizes which are to be awarded to members of the fourth year class of George Washington and Georgetown Medical Schools for excellence in Pediatric theses.

Torrioli and Puddu (3) conclude that a similar principle also exists in normal spleens but that it is less active in injuring the megakaryocytes. They seemed to think that this principle is capable of injuring the megakaryocytes in high doses and of stimulating them in low doses. It is probable that the principle exceeds normal concentration in purpura. Hobson and Witts (4) were also able to extract this substance from normal spleens but found that Ringer's solution gave a more powerful extract than did acetone. The thrombopenic factor could not be found by Watson (5) and he suggests that the positive results previously obtained by others might be attributed to a non-specific reaction to the intravenous injection. Anaphylaxis or a histamine-like reaction has been postulated by Uihlein (6).

Rose and Boyer (7), and Paul (8) confirm the presence of a platelet reducing substance. The latter investigator found a rapid, marked rise of platelets in his laboratory animals following splenectomy. This, he believes, points to a maturation arrest of megakaryocytes and therefore to a lack of platelet formation rather than to a destruction of platelets. Otenasek and Lee (9) were also able to repeat successfully the work of Troland and Lee. They suggest that several types of idiopathic thrombocytopenic purpura may exist and thus explain the disparity in the results of other investigators.

The fact that a lowered capillary resistance exists in this disease was brought to light again by Elliot (10) in his report that the capillary resistance tends to follow the severity of clinical bleeding more closely than does the blood platelet level. At a later date, Elliot and Whipple (11) produced an experimental purpura, with the spleen playing a minor rôle, by using anti red cell serum to injure the capillaries and agar serum to reduce the platelets. Either serum alone would not produce the condition. It is believed that both a capillary and a platelet factor exist and that the capillary factor is the more important one. Since the capillary resistance rises so dramatically following splenectomy, they agree that the rôle of the spleen in the clinical form of the disease is of prime importance.

That there is some disturbance in the degradation of cystine leading to faulty clot retraction was reported by Rabinowitz (12). The failure of cysteine to conjugate with cholic acid in poor liver function leaves cysteine to reduce the —S—S— linkages of thrombin. Most of the sulfur in thrombin must be in the —S—S— form or a disturbance in clot retraction will result. He considers the influence of amino acids in controlling spontaneous bleeding and clot retraction to point to the impairment of liver function. The amino acid most effective was methionine.

In passing, the question of allergy should be raised as a possible etiologic

TABLE 1

CASE	COMPLAINT	FINDINGS
1. 19 mo. WM 1st adm.	Irritability, frequent epistaxis, easy bruising.	Several ecchymotic areas, spleen 3½ cm. below left costal margin & liver 1½ cm. below right costal margin.
2nd adm.	In for treatment.	Several bruises, large posterior cervical lymph nodes.
2. 3 yr. WF 1st adm.	Weakness, had been falling down easily.	History of purpura, few ecchymoses, pallor, muscular weakness of right upper & lower extremities.
2nd adm.	Purpura, fever, emesis, anorexia, dyspnea.	Temperature 101–102. Death on 2nd hospital day.
3. 5 yr. WM	Pain in right thigh.	Anxious expression, tender right thigh, many ecchymotic areas on lower extremities.
4. 14½ yr. WM	Black and blue marks.	Many petechiae & ecchymoses on skin and mucosa.
5. 7 yr. WF	Easy bruising, sore knee joints.	Tender knee joints, petechiae and ecchymoses over lower extremities. Spleen 2 cm below costal margin.
6. 14 mo. WM	Generalized black and blue spots.	Numerous ecchymotic areas of skin and mucosa. Frank bleeding from 2 teeth.
7. 6 yr. CM	URI and purpura. History of purpura 2 years ago.	Few ecchymotic areas. Right lower lobe pneumonia. Temperature 104° on admission.
8. 9 yr. WF	Bleeding from gums and subcutaneous tissues.	Diffuse petechial and purpuric spots, evidence of bleeding from gums, slight enlargement of cervical lymph nodes.
9. 6 yr. WM	Mass in left upper quadrant. History of purpura.	Visible and palpable mass in left upper quadrant.
10. 18 mo. WM	Fretful, edema.	Pallor, anemia, slight edema of palpebral tissue.
11. 4 yr. WF	Red spots on back and lips.	General petechial and purpuric areas.
12. 2 yr. WM	Anemia, red spots on skin.	Diffuse petechial rash, enlarged parotid gland. Several bruised areas, spleen 3½ cm below costal margin.
13. 4 yr. WM	Multiple bruises.	Several ecchymotic areas, liver slightly enlarged.
14. 5½ yr. WM 1st adm.	Black and blue spots. Always bruised easily.	Purple ecchymotic spots.
2nd adm.	Purpura and URI.	Purpuric spots on lower extremities and mild coryza. Pallor.

TABLE 1—*Continued*

CASE	COMPLAINT	FINDINGS
15. 4 yr. WF	Purpuric spots.	Generalized ecchymotic areas.
16. 6 yr WM	Emesis, fever, spots on the face.	Petechiae on forehead and face only.
17. 14 yr. WM	Easy bruising.	Generalized petechiae and ecchymoses of the skin and mucosa.
18. 14 day WF 1st adm.	Vomiting, retching, inability to take complete feeding. History of "blue spells."	Bulging fontanelle. Diagnosis of intracranial hemorrhage.
2nd adm.	Size of head increasing. High pitched cry.	Bulging fontanelles. Diagnosis of block in the ventricular system. Suboccipital decompression done. Patient died.

factor in the essential form of purpura, especially when patients fail to respond to general measures of therapy (13).

Pathology

From Boyd (14) we learn that examination of the spleen usually reveals the germinal centers of the lymph follicles to be large and active. Empty sinusoids with swollen lining epithelium are also seen. Hyaline megakaryocytes, present only in this disease, are said to produce the large pseudoplatelets. A characteristic finding is supposed to be the presence of megakaryocytes in the splenic and liver sinusoids and in the capillaries.

Phillips and Zionts (15) state that there is an endothelial proliferation of the Malpighian bodies and sinuses with an increase in the number of reticulum cells in the spleen. There is an infiltration of eosinophils and megakaryocytes and one occasionally sees a phagocytosed thrombocyte. The bone marrow may show aplasia with megakaryophthisis and an anemic response of the erythrocytes. In some cases there may be an increase of megakaryocytes with many young forms and poor budding of the platlets.

In general, however, necropsy findings in essential thrombocytopenic purpura are usually disappointing (16).

Signs and Symptoms

The foremost complaint in most cases is that of easy bruising (1, 15, 16, 17, 18, 19, 20, 21). Hemorrhage may occur into the skin, mucous membrane, or any internal organ. Common sites for bleeding to take place are from the nose and the gastro-intestinal tract. In the acute

forms, there are usually no petechiae or ecchymoses but a sudden onset of bleeding from the mucosa. An acute attack is rarely fatal except in severe fulminating cases.

Chronic cases may have these features: anemia, fatigue, weakness, a history of easy susceptibility to trauma with purpuric spots, and periods of remission when the patient is apparently well. Anemia is secondary and never in excess to the amount of blood lost. The white cell count may be normal or may show a slight leukocytosis at times; leukopenia usually speaks against the diagnosis of purpura. Petechiae and ecchymoses vary in size and shape and show no sites of predilection. Fever is usually not a factor but may be present in the acute forms.

There may be slight splenomegaly but marked enlargement of the spleen should cast doubt upon the diagnosis. It is very rarely palpable.

The following table gives some idea of the complaints and findings encountered in the eighteen cases reviewed at Children's Hospital.

The diagnosis in all these cases was confirmed by laboratory examinations and tests.

Laboratory Findings

Platelets are decreased in the majority of cases. Spontaneous hemorrhage occurs usually when the count falls to 40,000 per cu. mm. or below (22). However, in chronic cases the platelets may be normal or only slightly reduced in numbers, but, the lowered capillary resistance and the tendency to bruise remains (14).

The bleeding time is increased and the clot retraction is prolonged or absent, while the prothrombin time and the coagulation time are normal (14). Some (23), however, believe that there is a moderate or marked hypocoagulability of the blood plasma. Their basis for this belief is the reduction in the number of platlets resulting in a quantitative deficiency of thromboplastin.

Capillary resistance is also decreased in this disease (9, 10, 14). The tourniquet test may be used to determine the resistance of capillaries.

Bone marrow studies vary and it is doubtful if they show any significant characteristics (19).

In the cases reviewed, the platelet counts showed wide variations throughout the hospital course. The average count on admission was 53,000/cu. mm. All except four showed a varying degree of secondary anemia. The average leukocyte count was 7500. The coagulation time averaged 3 minutes and the bleeding time averaged 3.8 minutes. Bone marrow studies varied a great deal from total absence to increased numbers of platelets, etc

Diagnosis

As in all conditions, a good careful history should be taken. Kracke (24) states that in all cases of purpuric disorders the following tests or examinations should be carried out: a complete blood count, a platelet count, coagulation time, bleeding time, tourniquet test, clot retraction test, prothrombin time, and plasma fibrinogen estimation in some cases. A bone marrow examination is also important (14).

For diagnostic purposes, the main features of essential thrombocytopenic purpura are the history of easy bruising, purpuric lesions, the reduced number of platelets, increased bleeding time, poor or absent clot retraction, decreased capillary resistance, and normal coagulation and prothrombin times.

Differential Diagnosis

It is very important to distinguish the essential from the secondary purpuras since both may have a thrombopenia (12, 14, 15, 16, 19, 21).

Certain drugs may cause purpura including sulfonamides, gold salts, sedormid, benzene, arsenicals, coal tar products, benzol compounds, etc. Those of lesser importance which have been reported are: phenobarbital, dinitrophenol, quinine, bismuth, ergot, and iodine. Thus, it is quite apparent that careful questioning of the patient or his parents is very important in arriving at a correct diagnosis.

Typhoid fever, measles, small pox, meningococcic septicemia, typhus fever, miliary tuberculosis, and subacute bacterial endocarditis are among the more important infectious diseases responsible for purpura in some instances. A thorough history and physical examination along with the necessary laboratory adjuncts to diagnosis should exclude any of these conditions.

Vitamine C deficiency may be the cause of hemorrhagic lesions, etc.

As has been stated before, allergy to foods and other substances must be ruled out as a possible etiologic factor.

Purpura is common in aplastic anemia and leukemia. In the former there is a marked reduction in both erythrocytes and white cells. The anemia which is present is out of proportion to the blood loss whereas, in purpura, the anemia parallels the amount of blood lost only. A differential white count may reveal a lymphocytosis. In cases of leukemia, the key finding is that of numerous immature white cells. Ulcerative lesions of the mucosa, glandular enlargement, and the severity of the disease should leave little doubt as to the diagnosis. Bone marrow smears are of utmost importance in both of these conditions.

Pernicious anemia may show purpuric lesions but, of course, this disease is not found in children.

Hemophilia should not be confused with purpura. It shows prolonged coagulation and prothrombin times with normal bleeding times, normal clot retraction, and normal numbers of platelets. Here, also, there is a marked hereditary tendency with only males having the disease.

Sako (16) gives us a concise table which is of value in the differential diagnosis:

Henoch's and Schönlein's purpura may be confusing but should leave little doubt in the mind of the examiner when the laboratory examinations are found to be essentially normal. Other anaphylactoid purpuras are to be distinguished by their normal platelet counts, etc.

It has been stated that marked splenomegaly speaks against the diagnosis of purpura hemorrhagica; so, diseases associated with marked splenic enlargement should not confuse the examiner.

TABLE 2

HEREDITARY	SEX	COAGULATION TIME	BLEEDING TIME	CLOT RETRACTION TIME	PROTHROMBIN TIME	PLATELETS	WBC
Hemophilia	Male	Marked increase	Normal	Normal or poor	Increased	Normal	Normal
Hemorrhagic disease	Both	Increased	Increased	Normal	Increased	Slight decrease	Normal
Leukemia	More male	Normal or increase	Normal or increase	Normal or poor	Normal or increase	Normal or decrease	Abnormal
Essential thrombocytopenic purpura	Both	Normal	Increase	Poor	Normal	Greatly decreased	Normal

One should be aware of the fact that x-ray and radium may cause purpura. Also, tumors of the bones may affect the hemopoietic tissue.

Prognosis

It has been said that 80 per cent of acute cases do become chronic, and that only 35 per cent of cases occurring during infancy survive (18). The general outlook after infancy, however, is said to be good (18). During childhood the disease tends to be self-limited with spontaneous recovery (20). One should be familiar with the fact that the initial episode may be the only one to occur during a lifetime, especially in children, even though the tendency of the disease in untreated cases is to pursue a cyclic course marked by remissions and exacerbations (22).

Schwartz (25) has shown that an increased eosinophil count of the bone marrow signifies a good prognosis for spontaneous recovery. A chronic course is expected when decreased numbers of eosinophils are found. He was unable to show any correlation between marrow eosinophilia and

peripheral blood eosinophilia. Likewise, there seemed to be no correlation between the clinical course and the peripheral blood eosinophilia in the cases reported in this article.

Treatment

The first and most important procedure in the treatment of idiopathic thrombocytopenic purpura is the correct diagnosis (17). This is accomplished by excluding all factors known to cause purpura (20).

Splenectomy appears to be the treatment of choice. The doctor is not justified in using conservative therapy alone in the splenectomy group; watchful waiting plus the postponement of surgery invites disaster (26). Indications for splenectomy are: 1) severe chronic cases (27), 2) when the bone marrow eosinophilia is reduced (25), 3) recurrent hemorrhage with the platelets below 60–75,000 per cu. mm. (28), 4) during first attacks when the platelet count does not rise after transfusion and bleeding persists (28).

The condition of the patient must be built up pre-operatively; anemia has to be corrected by adequate blood transfusions (17). Before surgery the platelets should number 100,000 per cu. mm. (26) and the erythrocyte count should reach 3.5 million (27). It is more favorable to operate after the acute attack (22) or during a period of remission (20, 22, 27). Dehydration should be corrected before surgery by the administration of molecular calcium lactate or Hartman's in distilled water (17). Vitamin K and bile salt therapy may and probably should be given on an empirical basis (17). In removing the spleen one must be certain that there are no accessory spleens to cause hemorrhage post-operatively (15, 17, 29). The risk of surgical hemorrhage is not as great as one might expect (22). One report lists the mortality in chronic cases as being 8 per cent and 70–80 per cent in acute cases (15). However, it is a good idea to have citrated blood ready during the operation and also to give prophylactic transfusions for several days post-operatively (17).

Vaughan and Wright (30) report complete cures for 5 to 15½ years following splenectomy. In properly selected cases, splenectomy appears to be a very effective method of therapy. Failures may be due to accessory spleens (29) or to inadequate diagnosis (24).

Ligation of the splenic artery is a more conservative method of treatment but splenectomy is considered far superior (31).

X-ray has been used on some patients but this method is not too satisfactory (15, 19, 32, 35). Bassin (34) found it to be of no value at all. Moderate or large doses may produce long remissions (33). The dosage is usually 200r every day or every other day for 6–12 doses (33). Since the splenic position varies, an irradiation field of 10–15 cm. should be used (33).

Repeated blood transfusions are of definite value for the anemia produced by blood loss (19, 32). The amount and frequency of transfusion depends upon the degree of anemia. Its use pre-operatively has already been discussed.

Moccasin snake venom is used sometimes (19, 35, 36). A dilution of 1:3000 is used and ½–1 cc. is injected at 2–5 day intervals for 10–15 doses. To judge any clinical improvement, the intradermal test is employed. With improvement it becomes negative. This method of therapy has not found wide usage and most investigators believe it to be of little or no value.

The "Fat Soluble T-factor" present in sesame oil and diets rich in lipids has been tried (19). It is of little value.

Vitamin C, calcium, adrenalin, various protein substances such as milk, horse serum, peptone, antivenin, and thromboplastin and parathyroid hormone are of no value (15, 19).

Liver and iron have some virtue in post-hemorrhagic anemia (21).

Two of the 18 cases were treated by splenectomy. Using the platelets as indicators, it would appear that this method of therapy is far superior to transfusion and medical treatment alone.

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SPECIAL REPORT

ERYTHROBLASTOSIS FETALIS[1]

Citing an Interesting Family History

Drs. J. D. Relfe and J. C. Adams

Levine and Stetson in 1939 reported the possibility of isoimmunization as the cause of erythroblastosis fetalis. In 1940 Landsteiner and Wiener working with the Rhesus monkey named the antigen present in the red cells of the monkey, the Rh factor. Later it was found a similar antigen caused erythroblastosis fetalis in humans. It has subsequently been postulated (1) that erythroblastosis fetalis may be caused by isoimmunization to the antigens A and B present in the erythrocyte and Levine (2) describes cases of erythroblastosis fetalis due to the Hr factor.

The recent importance laid upon the determination of the Rh factor in the practice of Pediatrics and Obstetrics seems well justified because of the untoward reactions which may result from sensitization to the Rh antigen. These reactions include transfusion accidents, anemia and jaundice in the mother, still-births and abortions, toxemias and the syndrome, erythroblastosis fetalis.

The determination of the Rh factor is becoming increasingly more extensive because of the availability of the Rh serums. The practice of testing for Rh subgroups is still not carried on by most laboratories and further investigation is necessary to determine the advisability of this as a universal procedure. Transfusions without determination of the Rh factor in all females has been condemned by Levine (3) because of the possibility of isoimmunization resulting in the aforementioned reactions. In all mothers delivered of infants presenting any of the symptoms of erythroblastosis fetalis determinations should be made in the mother, father and infant because of the possible necessity of transfusion being required in either mother or infant. The universal determination of the Rh factor would lessen the occurence of erythroblastotic infants in primiparae due to sensitization to the antigen.

It has been reported that approximately 85 per cent of the white population is Rh positive and the remaining 15 per cent Rh negative. The Rh antigen follows the Mendelian law as a dominant gene not sex-linked in transmission. In 90 per cent of cases of erythroblastosis fetalis the mother is Rh negative, the father and child are both Rh positive. The remaining

[1] This paper was submitted in competition for the Mead Johnson Prizes which are to be awarded to members of the fourth year class of George Washington and Georgetown Medical Schools for excellence in Pediatric theses.

10 per cent of cases may be explained partially on the basis of isoimmunization to the A and B antigens and partially by Hr reactions. Twelve per cent of all marriages occur between Rh negative females and Rh positive males and on this basis one would expect a great incidence of erythroblastosis fetalis whereas the actual incidence is only 0.1 per cent of all pregnancies (4).

In the great majority of cases it appears that the mechanism of action to produce erythroblastosis fetalis is the isoimmunization of the mother by the passage of Rh positive antigens found only in the erythrocytes of the fetus probably through the placental barrier to the mother's blood stream. The mother may react producing anti-Rh agglutinins which may return to the fetal blood stream producing agglutination or hemolysis of the fetal red cells. The same mechanism may occur by the passage of A and B antigens from the fetus to a mother of a different blood group (1). It has been noted that the A and B antigens occur in the red blood cells, somatic cells and in the sera. The low incidence of erythroblastosis fetalis reported due to the above mentioned mechanism seems to be due to a "protective mechanism". This "protective mechanism" results in the combination of antigen-antibody in the sera and therefore tends to prevent pathologic changes. The Rh antigens do not appear in the sera and therefore this "protective mechanism" does not prevail in cases of erythroblastosis fetalis (1).

The factor was named Hr because it was found in all Rh-negative blood which is the opposite of the Rh factor. Erythroblastosis fetalis due to the Hr factor occurs when both the mother and the child are Rh-positive. Hr negativity is determined by the Rh subgroups Rh_1 and Rh′ or a combination of them. All other subgroups of Rh-positive bloods as well as all Rh-negative blood is Hr-positive. It therefore follows that the mother who must be Hr-negative must have Rh_1 or Rh′ genes while the child who will receive one Hr-negative gene from its mother must have an Hr-positive gene as the companion if erythroblastosis fetalis is to occur (2).

Heretofore it had been believed that there was no admixture between maternal and fetal bloods. To produce erythroblastosis fetalis admixture of blood appears necessary though minute in amount. It has been postulated that admixture of blood may occur by an infarct into the placenta, by placental tear or by separation (partial) of the placenta and the aforementioned transfusion mechanism. It seems probable that the ability to pass the antigen through the placenta to the mother and conversely to pass the agglutinin through the placenta to the fetus varies in different individuals. It is also possible that there is a variance in different mothers' ability to produce antibodies. All of which would help to explain the relative infrequency of the syndrome. It has also been found that anti-Rh

agglutinins can pass from the mother to the infant through the breast milk.

There are three clinically recognizable forms of erythroblastosis fetalis: (a) hydrops fetalis in which there is anasarca and great enlargement of the liver, spleen and heart, (b) icterus gravis neonatorum, in which there is an increasing jaundice from birth, spontaneous hemorrhages, and a moderately enlarged spleen, (c) anemia hemolytica neonatorum, in which there is a severe anemia occuring within a few days after birth without either icterus or hydrops.

In treating a case of erythroblastosis fetalis it is now popularly thought that transfusion of the infant with Rh negative blood at first and later with compatible Rh-positive blood is the therapy of choice. However, other investigators believe that the use of Rh-positive blood as well as Rh-negative blood from the beginning may be more advantageous. They state that the anti-Rh agglutinins in the infant circulation must combine with Rh-positive cells in order to be inactivated. The rationale behind giving Rh-positive blood is to neutralize the antibodies quickly and therefore allowing the infant's own blood cells to carry on their normal function at an earlier date. The Rh-negative blood is given in conjunction until this takes place.

Case Report

This is the case history of the Negro family of J. and M. L. and their ten children. The mother is blood group A, Rh-negative. The father is blood group O, Rh positive homozygous of the subgroup Rh_0. As far as can be ascertained, the first seven children were spontaneous deliveries with no untoward reactions in the children or mother. All the children were born at home. The eighth delivery resulted in a normal child but excessive bleeding ensued in the mother. Shock developed in the mother necessitating hospitalization in Gallinger Municipal Hospital, Washington, D. C. While in Gallinger Hospital the mother received five blood transfusions which consisted of blood not typed for the Rh factor. Continuous chills were noted after the administration of the blood.

The ninth child, M. L., was seen at Childrens Hospital on September 1, 1943, five days after birth when jaundice suddenly appeared. The Van den Bergh reaction quantitatively was 14.4 mg. per cent with an icterus index of 100 units. The hemoglobin determination was 11 grams and the erythrocyte count was 2,600,000. The leucocyte count was normal. The child was discharged on September 11, 1943 as recovered. On January 15, 1945 the child was re-admitted to the hospital because of an upper respiratory infection. Upon physical examination evidence of upper motor neuron damage was elicited. An unstable psyche appeared manifest. The pneumoencephalographic report of the skull demonstrated some cortical atrophy. The child was found to be Rh-positive and the mother Rh-negative at this time. A diagnosis of Kernicterus following erythroblastosis fetalis was made in this case.

The blood groups and the Rh determination of the ten children and parents are as follows:

NAME	BIRTH DATE	BLOOD GROUP	Rh DETERMINATION	CONDITION
1. Ralph L.	1928	O	Rh positive, Rh_0rh	Good
2. Wilbur L.	1929	O	Rh positive, Rh_0rh	Good
3. Barbara L.	1930	A	Rh positive, Rh_0rh	Good
4. John L.	1931	O	Rh positive, Rh_0rh	Good
5. Marie L.	1932	A	Rh positive, Rh_0rh	Good
6. Rosemary L.	1936	O	Rh positive, Rh_0rh	Good
7. Phidias L.	1938	O	Rh positive, Rh_0rh	Good
8. Margaret L.	1939	O	Rh positive, Rh_0rh	Good
9. Michael L.	1943	A	Rh positive, Rh_0rh	Jaundice on 5th day
10. Maria Teresa	1945	O	Rh positive, Rh_2rh*	Jaundice on 1st day
J. L., father		O	Rh positive, Rh_0Rh_0	
M. L., mother		A	Rh negative, rh rh	

* The Rh determination in the tenth child was Rh-positive, Rh_2rh. The reason for this is undetermined at this time. The possibilities are: (a) the father of the tenth child is different than the father of the other nine children—the mother states that this is not a possibility, (b) the Rh determination of the child's blood is faulty, (c) the Rh determination of the father's blood is faulty.

During the years 1932–1936 and 1939–1943 no conceptions took place due to the practice of the Rhythm method of birth control.

The tenth child, M. T. L., born on March 31, 1945 was admitted at Gallinger Hospital on April 4, 1945 with jaundice. The infant was listless, ate poorly and diarrheal stools developed. The icterus index was 273 units, the hemoglobin was 43 per cent. The erythrocytes were 1,700,000 per cubic millimeter. The white cell differential showed a decided shift to the left. There was evidence of poikilocytosis in the erythrocytes. On discharge on May 6, 1945 the laboratory findings were: 51 per cent hemoglobin, 2,700,000 erythrocytes and an icterus index of 32 units.

The mother on admission to Gallinger Hospital following the birth of the tenth child was in shock. Delivery was spontaneous. There was a normal delivery of the placenta without excess bleeding. Laboratory findings revealed a red cell count of 2,360,000, white cell count of 26,000, icterus index of 33 units and urinary albumin was three plus. The total protein was normal. The patient was transfused with 500 cubic centimeters of *Rh-positive* blood. Physical examination revealed icteric sclerae (the husband had noticed jaundice in the patient a day or two before delivery),

a liver palpable three fingers below the costal margin and a spleen which was slightly palpable. On discharge a month later, the red cell count had risen to 4,410,000. The white count was 4,950 and the icterus index was 9 units.

In reviewing this case three interesting points should be brought out (1) the possibility of an Rh-negative mother and an Rh-positive father conceiving eight perfectly normal children, (2) the danger of transfusing an Rh-negative woman with undetermined blood, which may result, as is probable in this case, in the development of erythroblastosis fetalis in the following children and (3) the syndrome, erythroblastosis fetalis appears to increase in severity with each subsequent pregnancy.

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Case Report No. 33

ARTHROGRYPOSIS CONGENITA

Dr. Sydney Ross P. B.—41-7204

P. B., a 12 year old white female, was admitted to Children's Hospital on December 12, 1941 with a chief complaint of deformities of the extremities and inability to walk. The hands, arms, thighs, legs, and feet were noted to be abnormal at birth. The patient was hospitalized at the age of six weeks and remained institutionalized during the next five years at the Crippled Children's Hospital, Richmond, Virginia, where a diagnosis of arthrogryposis congenita was made. In April 1931, a double plaster spica cast was applied for correction of deformities of the lower extremities and she remained in the cast for 3 months without any perceptible improvement noted. Gross deformity of the extremities remained essentially unchanged during the next 10 years. In 1941, the child was admitted to the Shriner's Hospital for Crippled Children in Philadelphia where a similar diagnosis was entertained.

Past history revealed that labor was apparently normal and the infant weighed 8 lbs. at birth. She took her feedings well and gained weight normally. The patient had measles at the age of five and has had frequent upper respiratory infections. The parents are living and well and two siblings are in good health. A third sibling died at birth of congenital heart disease. As far as is known, there is no family history of any muscular dystrophies.

Physical examination on entry revealed a fairly well nourished white female with multiple deformities. The hands were very small and there was some webbing and approximation of the thumb and fifth fingers. A scaling erythema was noted on each palm. The arms and forearms were thin, showing considerable muscular atrophy. Movement of the elbows, wrists and fingers was very limited and motion was transmitted to the upper extremities mostly through the shoulders. The forearms were hyperpronated to such a degree that the palms pointed laterally. The lower extremities were flexed at the thigh and knee with very little motion being present in the legs. Operative scars were present over the medial aspects of both knee joints. The feet were small, the great toe being inordinately large in comparison to the other toes. There was no appreciable motion of the feet or toes. Considerable atrophy of the quadriceps and gastrocnemii was noted and there were trophic changes in both palms and feet. The neck and shoulder girdle appeared normal A marked lordosis was present.

Neurological examination revealed the cranial nerves to be normal The biceps and radial reflexes were not elicited. Knee jerks were present but were bilaterally hypoactive. Babinskis were normal. Sensory modalities including pain, touch and temperature were normal over the entire body and extremities. There appeared to be no gross mental

FIG. 1

retardaton. The remainder of the physical examination was essentially negative.

The blood picture was within normal limits and the urinalysis was negative. Roentgenological examination of the skull, cervical spine and chest revealed no evidence of abnormality. Blood Wassermann was negative.

Consultation with Drs. Washington and Litvin was obtained and it was thought that the deformities were compatible with a diagnosis of arthrogry-

posis congenita. The child was discharged from the hospital after a two week study and has been followed in the out patient department since then. During the past four years there have been no singular complaints except for occasional bouts of palpitation coming on chiefly at night. Electrocardiogram and heart films have revealed nothing remarkable and the etiology of the tachycardia was thought to be psychogenic in origin.

Discussion

Arthrogryposis congenita is an appellation used to denote symmetrical joint rigidities which are congenital in origin. Synonymous terms include amyoplasia congenita, and multiple congenital articular rigidity. In choosing the name "Arthrogryposis," Lewin (1) in 1925 proposed that the joints were primarily at fault. This concept, however, has been questioned by Sheldon (2) who believes that the primary defect in this syndrome is a failure of muscular development, having its origin in utero, and that the defects in the joints were a secondary manifestation. He was able to show that in testing the electrical reaction of the affected muscles, there was weak or absent faradic responses. The term "Amyoplasia" was suggested by Sheldon as being more descriptive of the defect in this symptom complex.

The diagnostic criteria of Arthrogryposis proposed by Cook (3) include the following:

1. Congenital joint rigidities of varying degrees usually symmetrical, and always without inflammatory changes.
2. Hypoplasia or degeneration of those muscles which normally produce the movements which the child is able to perform.
3. Absence of any hypertonia and hypertrophy of antagonistic muscles, showing that the immobility is not attributable to muscle overaction.
4. Weak or absent faradic responses in affected muscles, with no reaction of degeneration.
5. No sensory or trophic changes.
6. Normal intelligence.
7. Extensive fibro fatty changes in the affected muscles.

Altman and Davidson (4) report a case with bilateral ptosis as an accompanying feature.

The case presented here satisfies the majority of criteria proposed by Cook.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: Dr. E. Clarence Rice

Assisted by: Drs. John E. Cassidy and Robert Sullivan

PANCREATIC FIBROSIS

Case Report No. 34

Dr. Robert Sullivan A. B.—45-3515

A. B., a nine weeks old white male, was admitted to the hospital on April 30, 1945 because of coughing for one month. The infant was sent to the hospital by a physician who had been called the preceeding evening when apparently the formula had been aspirated causing deep cyanosis. Coughing had been present for about one month and had become considerably worse during the last two weeks. His mother had noted "expiratory noises" in his chest. The past history was non-contributory. The parents and a three year old sibling were in good health.

The physical examination revealed a rather undernourished and chronically ill looking infant with a swarthy complexion and a clear cool skin. The right ear drum was injected. Respirations were rapid and there were diffuse crackling rales over the right base posteriorly. Breath sounds were harsh and intense bilaterally. The rest of the examination was negative. The temperature on admission was 99.0°. The weight was 8 pounds 13 ounces. The complete blood count showed a hemoglobin of 9 grams, a white blood cell count of 9,400 with 55% segmented forms, 5% band forms, 37% lymphocytes and 3% monocytes. A blood culture taken on admission was negative.

The admitting diagnosis was bilateral bronchopneumonia and steam inhalation and sulfadiazine were administered. A chest x-ray taken on the first day showed an opacity over the entire left chest with retraction of the mediastinum towards that side. This had the appearance of a massive collapse. Three days later an x-ray revealed partial clearing on the left with an opacity in the right apex with a shift of the mediastinum to the right. Two days later the opacity in the right apex had undergone complete resolution, the left chest was aerated but showed diffuse mottling and the mediastinum was almost in the mid-line.

From the fourth day of hospitalization on, an oxygen tent was used constantly because of dyspnea, cyanosis and coughing. The temperature range was from 97.8° to 100.5°. Feedings were for the most part taken well with infrequent vomiting. There were from one to six stools daily usually soft and yellow-green but on three occasions gray or white. The

weight curve was steadily downward from 8 pounds 13 ounces to 7 pounds on the forty-fifth day.

On the eleventh day penicillin replaced sulfadiazine therapy but no clinical response was noted. In spite of parenteral fluids and supplementary vitamins the infant's condition slowly became worse.

An x-ray one month after admission revealed mottled infiltration throughout the left lung which had the appearance of multiple abscesses. There was considerable emphysema on the right.

Six weeks after admission the infant died.

Clinical Diagnosis

1. Cardiac failure and toxemia
2. Bilateral bronchopneumonia
3. Pulmonary atelectasis.

Necropsy Summary

The trachea and bronchi contained a large amount of viscid, greenish yellow purulent material. The smaller divisions of the bronchi were somewhat dilated and also contained this purulent material. The lungs were voluminous and emphysematous except the greater portion of the upper left which was atelectatic and of a rose color containing miliary abscesses. The right upper lobe was atelectatic to a lesser degree. Firm areas were scattered through all the lung tissue and when sectioned were found to be airless and the sites of miliary abscesses.

The pancreas weighed 3.5 grams. It was firm and shotty, the lobules being small and irregularly shaped. It sectioned with increased resistance revealing an irregular cut surface. Microscopic sections of the pancreas showed considerable distortion of the acinar tissue because of increased interstitial fibrous tissue. The acinar ducts, some of which were dilated, contained a homogeneous basophilic material. The islet tissue was relatively normal except for some spacing of the cells and vacuolization.

Pathological Diagnosis

1. Malnutrition
2. Multiple abscesses of the lungs
3. Pulmonary atelectasis
4. Bronchiectasis
5. Fibrosis of the pancreas

Discussion

Dr. Harold W. Spies: Cystic fibrosis of the pancreas is primarily a disease of infancy which up until a few years ago was described by the

pathologist but the real significance was unknown. In 1938 Anderson succeeded in correlating the pathology with the clinical manifestations and cystic fibrosis of the pancreas became a distinct entity.

Clinically the disease is characterized by failure to gain weight, wasting, distended abdomen, copious foul stools, vomiting, excess fat in the stools, absence of pancreatic trypsin and lipase from the duodenal juice and a flat type of glucose tolerance curves and Vitamin A tolerance. In a series of 1000 autopsies at Babies Hospital Anderson found 20 cases of cystic fibrosis of the pancreas. The pancreas was sectioned in 605 of the cases and thus an over all incidence of this disease appeared to be about 3%.

Anderson's classification of the disease includes:

Group one comprising about 10%. This group usually dies of intestinal obstruction due to meconium ileus.

Group two is made up of 60% who die before the sixth month of life due to respiratory pathology such as bronchiectasis and bronchitis with terminal pneumonia.

Group three is made up of those cases who live from six-months to fourteen years. This group is often confused with celiac disease and the patient may apparently do well on the usual celiac treatment.

Group four is that group who live normal lives and the cysts and fibrosis of the pancreas are discovered on postmortem examination.

The etiology of cystic fibrosis has not been definitely established. However, there are a few observations, the importance of which it is difficult to evaluate. A family tendency has been noted in this disease. There may be a history of a previous child who died early in life of gastro-intestinal or respiratory disease. The disease occasionally appears in siblings. Other congenital anomalies have been associated sometimes with cystic fibrosis. These include atresia or narrowing of the intestine, bronchi, bronchioles, ureters, kidney tubules, bile ducts and cystic ducts. These findings suggest the possibility that the pathology is that of congenital malformation. The possibility that a Vitamin A deficiency is a factor in the etiology of pancreatic fibrosis has been advanced. The question rises whether the Vitamin A deficiency is the cause of the disease or the effect in view of the presence of a deficiency of pancreatic enzymes with resulting impairment of fat digestion and absorption of fat soluble vitamins.

The pathological changes which occur in the pancreas are those indicated by the name of the disease, namely, the presence of fibrosis and cyst formation. The acinar tissue is replaced by cysts and the normal cuboidal type of acini lining cells appear as flattened epithelium. The cysts are surrounded by dense bands of fibrous connective tissue. The small ducts of the pancreas may be obstructed by inspissated secretory material resulting in distension of the acini. The Islands of Langerhans appear

essentially normal. In a few cases there is evidence of pathology in the liver with amyloid disease and fatty infiltration having been reported. The lungs in pancreatic fibrosis usually reveal pathological findings typical of bronchiectasis, bronchopneumonia, bronchitis or abscesses of the lung.

The laboratory findings are valuable aids in diagnosis. Analysis of duodenal drainage after stimulating the pancreas shows marked decrease in quantitative and qualitative secretory response, there usually being a marked diminution or absence of pancreatic trypsin and lipase. The stools contain a high percentage of neutral fats, the fat content often ranging between 50 to 75% of the dry weight of the stool. Both the Vitamin A tolerance curve and the glucose tolerance curve usually show diminished or absent absorption yielding a flattened curve. Blood cholesterol is low and there is usually an associated anemia.

X-ray of the chest usually shows evidence of bronchitis or bronchopneumonia.

Treatment of fibrocystic disease of the pancreas should include a diet which is high in protein and low in fat. The caloric intake should be 20 to 40% above average if the infant is able to tolerate it. Vitamin A given parenterally should be provided in adequate dosage. Similarly adequate supplements of Vitamin B, C, and D are indicated. Pancreatic enzymes given orally are indicated for replacement therapy. Blood transfusions and intravenous and subcutaneous fluids are important means of supportive and replacement therapy for diarrhea and vomiting. Chemotherapy including penicillin and sulfonamide drugs may be used in the treatment of the complicating bronchitis and bronchopneumonia.

The prognosis in pancreatic fibrosis is necessarily guarded. Frequently this disease is not diagnosed largely due to the lack of clinical symptoms. Cystic fibrosis occurs frequently enough to warrant consideration in the differential diagnosis of those children who show intolerance and failure to digest fat or those infants with chronic bronchitis, bronchiectasis or recurrent attacks of bronchopneumonia.

CLINICAL PROCEEDINGS OF THE CHILDREN'S HOSPITAL

Washington, D. C.

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Occasionally, the remarks and observations of guest speakers are included in this bulletin when thought to have particular interest. The proximity of the Children's Hospital to the Medical Centers of the Army, Navy and United States Public Health Service affords us the opportunity to invite many distinguished physicians to our conferences.

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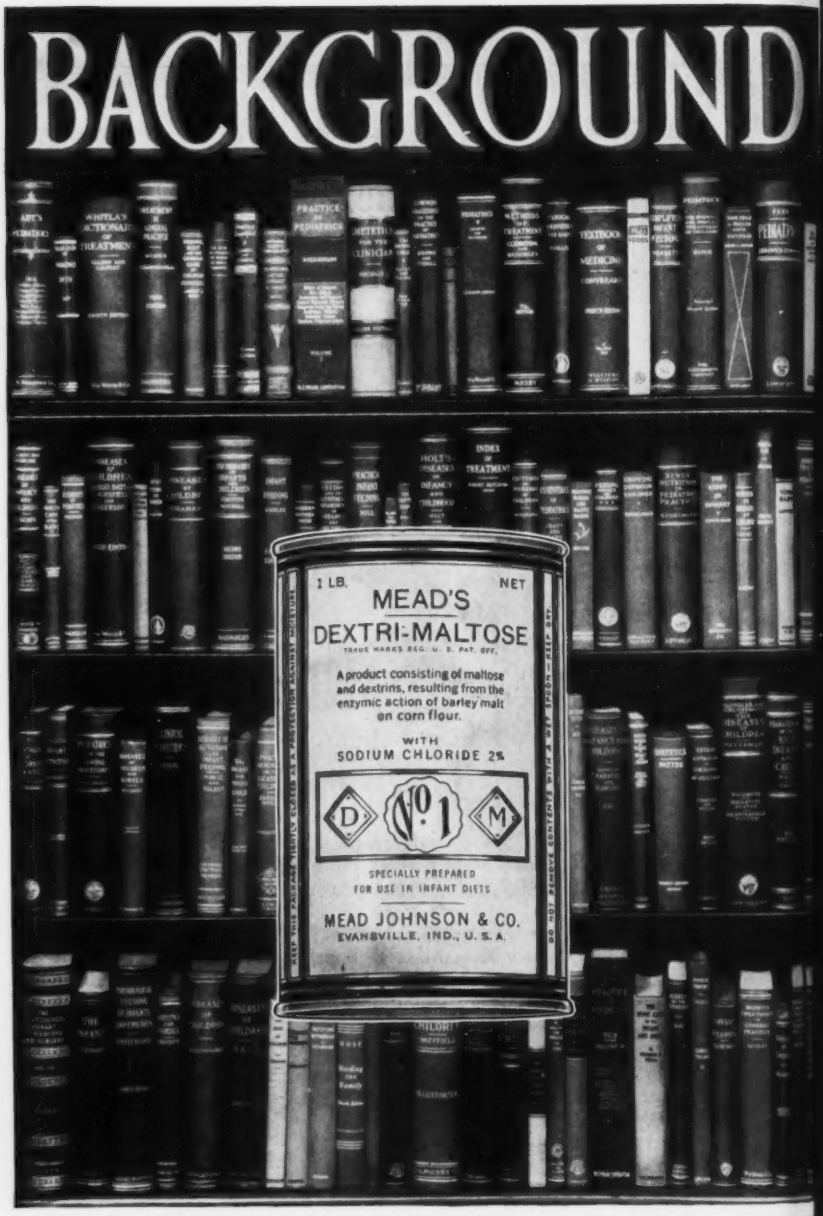
BACKGROUND



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